Plasma level of trace elements in patients with oral lichen planus

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Background: Oral lichen planus (OLP) is a common inflammatory disease of unknown origins. Recent studies have considered nutritional factors concerning the pathogenesis of many autoimmune disorders. The objective of the present study was to investigate the plasma levels of magnesium (Mg), calcium (Ca), zinc (Zn), copper (Cu), and iron (Fe) in this disorder.

Methods: Included in this observational case-control study was 40 patients with OLP and 40 age and sex matched healthy control subjects. Plasma levels of Mg, Ca, Zn, Cu, and Fe were specified using an autoanalizer.

Results: The serum level of Ca was higher, but Mg, Cu, Fe and Zn serum concentration did not differ significantly between the patients with OLP and the healthy controls. Mean Zn concentration was lower in patients with erosive lichen planus compared to the non-erosive group and the healthy controls. However, only the difference between erosive lichen planus patients and healthy participants was significant. The mean Zn level was lower than the normal range (70 µg/dl) in both the cases and controls. The concentration of Fe was significantly higher in men male patients than in females; however, the difference between men and women was not significant in the healthy control group. The mean Cu/Zn ratios in erosive and patient groups were slightly higher compared with the controls.

Conclusion: Trace elements such as Ca may play a role in the ethiopathogenesis of OLP. Nevertheless, other elements such as Zn or Cu may influence OLP, which requires further evaluation on larger samples.

Keywords: lichen planus, zinc, copper, calcium, magnesium, iron

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INTRODUCTION

Lichen planus (LP) is a chronic autoimmune disorder affecting the skin and mucous membrane. Although the disorder can involve several parts of the body, including skin, nails, and genital mucosa, it mainly appears in oral mucosa [1,2]. The estimated prevalence of oral lichen planus (OLP) ranges from 0.47% to 1.27%, and it is more common in middle-aged women than in men [3,4]. Patients may experience different clinical forms of OLP including reticular, papular, erythematous, ulcerative, and bullous [5,6]. The apoptosis of basal keratinocytes which is mediated by autoimmune T cells has been considered as the pathogenesis of OLP [1,7]. Several causative/exacerbating factors such as stress, diabetes, other autoimmune diseases, food, allergy, and trauma have been associated

with the pathogenesis of the disease. On the other hand, the exact etiology of this autoimmune disorder is yet to be fully clarified [8,9]. There are findings suggesting the possible role of trace element imbalances in the pathogenesis of several diseases [10]. Trace elements only make up a small amount of the body weight, but play a vital role in different biological mechanisms such as the immune system [11]. Moreover, copper (Cu), zinc (Zn), calcium (Ca), magnesium (Mg), and iron (Fe) play important roles in various biochemical reactions. Magnesium and zinc have significant impacts on cell growth, division, and differentiation [12]. Zn, Fe, and Cu affect antioxidant processes, such that the changes in these elements may cause the formation of reactive oxygen species (ROS) in the body (13,14). Many studies have corroborated the negative role of (ROS) in different autoimmune diseases and defensive functions of antioxidants [13,15-17]. Copper, as a cofactor for certain metalloenzymes, is required for normal cell homeostasis, optimum immune system, and overall health. Iron is important for many metabolic processes, and its deficiency impairs physical performance, immune function, and neurotransmitter system [18]. Apart from its crucial role in bone health, calcium is necessary for a normal function of the immune system as a messenger in many cell types [19]. Calcium is assumed to be the central regulator of keratinocyte differentiation [20]. Magnesium catalyzes and/or activates more than 300 enzymes [21], and is a vital element for growth and immune system [22]. According to our knowledge, there are few conflicting reports on the possible role of trace elements in oral lichen planus [23-26]. Therefore, due to the high prevalence of OLP, we aimed to measure the serum concentrations of Mg, Ca, Zn, Cu, and Fe along with Cu/Zn ratio and Ca/Mg ratio, to find their association with the disorder or its severity.

PARTICIPANTS AND METHODS

This case-control study was performed on oral lichen planus patients referred to the oral medicine department of Shiraz Dental School (Shiraz, Iran) between October 2015 and June 2016. The study protocol was accepted by Ethics Committee of Shiraz University of Medical Sciences, and each subject signed an informed consent form. The diagnosis was based on clinical examinations, where Wickham's striae had to be observed. However, a biopsy examination was carried out in patients with atypical lesions and/or possible dysplasia. Patients with suggestive signs of other lichenoid reactions such as contact lichenoid reaction and drug induced lichenoid reaction were excluded from the study. Further excluded were OLP patients who had other autoimmune or inflammatory diseases, and malignancies or epithelial dysplasia in the pathologic report, and those taking systemic drugs, vitamin or mineral supplements over the past two months. Ultimately included were 40 eligible patients (23-71 years old) and 40 age (± 2 years) and sex matched healthy control participants who were referred to Shiraz Dental School for routine dental works. The patients group was further subdivided into erosive and non-erosive oral lichen planus subgroups. Three ml venous blood samples were taken from all participants, and centrifuged for 10 minutes at 3000RMP. To specify the serum concentrations of the elements, the colorimetric method with commercial kits (Pars Azmoon, Iran) and an auto-analyzer (BioLis 24i Premium, Japan) were employed. SPSS software (version 15.0; SPSS Inc, Chicago, IL, USA) was used for statistical analyses. Results were analyzed using independent t-test, one-way ANOVA, and Pearson correlation test. P-value <0.05 was regarded as statistically significant.

RESULTS

To be matched, the patient and control groups were both comprised of 25 females and 15 males. There were two subjects with concurrent cutaneous involvement. In both case and control groups, there was one smoker participant. The mean age of the patients and the controls was 50.02±11.54, and 49.89±11.53 years, respectively. Table 1 shows the mean blood concentrations of copper (Cu), zinc (Zn), calcium (Ca), magnesium (Mg), and iron (Fe), and the ratios of Cu/Zn and Ca/Mg. The mean calcium level was significantly higher in patients than in healthy control participants (P=0.01). However, the differences were not significant regarding other elements (all P>0.05). Concerning the average serum levels of the studied elements, there was no significant difference between erosive OLP patients (20 patients) and non-erosive OLP patients (16 patients). (Table 2)

Table 1. The levels of trace elements in patient and control groups

Elements	Groups	
	Patients [mean±SD (min–max)]	Controls [mean±SD (min–max)]
Cu	97.15±21.88 (54–155)	105.43±21.70 (77–199)
Zn	62.80±15.25 (35–88)	69.10±14.93 (46–124)
Ca*	9.72±0.66 (8.5–11.6) *	9.41±0.33 (8.4–10.0) *
Mg	2.39±0.18 (2.0–2.8)	2.37±0.20 (2.0–2.7)
Fe	91.45±30.14 (33–148)	83.41±30.87 (33–170)
Cu/Zn ratio	1.60±0.42 (0.77–2.83)	1.57±0.40 (0.90–2.90)
Ca/Mg ratio	4.08±0.40 (3.44–5.09)	3.98±0.33 (3.42–4.70)

*Significant difference in the level of Ca in the patient and control groups (P = 0.013).

Table 2. Serum elements level in the erosive and non-erosive subgroups of disease.

Elements	Groups	
	Erosive [mean±SD]	Non-Erosive [mean±SD]
Cu	96.95±21.72	91.43±17.72
Zn	59.40±13.52	66.00±16.77
Ca	9.75±0.76	9.62±0.47
Mg	2.39±0.20	2.43±0.15
Fe	94.15±27.79	88.93±36.16
Cu/Zn ratio	1.66±0.46	1.43±0.30
Ca/Mg ratio	4.10±0.43	3.95±0.24

One-way ANOVA test was performed to measure the differences regarding the average serum concentration among the three groups (erosive patients, non-erosive patients and healthy subjects).

There was no significant correlation between the age and serum levels of the studied elements. There was a weak correlation (r=0.39, P=0.01) between Cu and Zn concentration in the case group.

As indicated in Table 3, the concentration of Fe was significantly higher in male than in female patients, a difference not significant in healthy controls. In both case and control groups, men had significantly lower copper/zinc ratios, compared with the corresponding values for women. Serum zinc also was less in women; however, it was not statistically significant in healthy subjects.

Table 3. Serum level of elements according to gender

Elements	Groups			
	Patients		Controls	
	Male	Female	Male	Female
Cu	83.73	99.08	103.68	106.65
Zn	67.80	58.79	75.63*	64.56*
Ca	9.57	9.81	9.51	9.35
Mg	2.39	2.42	2.43	2.34
Fe	105.67*	82.20*	93.00	76.73
Cu/Zn ratio	1.26*	1.72*	1.40*	1.70*
Ca/Mg ratio	4.03	4.08	3.94	4.01

DISCUSSION

Oral lichen planus is an inflammatory mucocutaneous disorder of unknown etiology. Despite the large research efforts, only few etiological factors have been determined for OLP [8,27-28]. Recent studies have drawn attention to the alteration in the serum trace element levels involved in the pathogenesis and progress of the disease [10,11]. To study this hypothesis, we investigated the plasma levels of magnesium, calcium, zinc, copper, and iron concentrations in patients with OLP. Micronutrients play essential roles in the immune system on the three lines of defense through supporting external barriers, cell-mediated immunity and antibody production [29]. Trace elements have also been reported to be crucial in numerous biological processes in the body [10].

Zn, a requisite for more than 300 enzymes [30], significantly influences the cell proliferation, especially the highly proliferating cells of epithelium and immune system. Gholizadeh et al. showed that Zn serum levels decreased significantly in OLP patients, and observed lower Zn levels in erosive OLP patients than in non-erosive OLP [24]. In Kleier's study, patients with oral lichen planus had no statistically significant difference with the controls concerning Zn values [26]. The present study revealed reduced Zn serum levels in the patients. The mean Zn concentration was lower in patients with erosive lichen planus, compared to the non-erosive group and healthy controls. However, only the difference between erosive lichen planus patients and healthy participants was significant. The mean Zn level was lower than the normal range (70 µg/dl) in both case and control groups,

which is in accordance with previous studies on the prevalence of zinc deficiencies [14]. Due to their high phytate content, cereal proteins, comprised of the main food portion in the developing countries, reduce zinc absorption. Decreased plasma zinc concentration is related to immunological dysfunction, increased oxidative stress and the generation of inflammatory cytokines [14]. Oxidative stress and chronic inflammation eventuate in many chronic diseases such as lichen planus [15].

Copper is required for the development and maintenance of the immune system [29]. As a component of many redox enzymes, copper has a key role in anti-oxidative processes [31]. Mean serum copper concentration did not differ significantly in the present study. To our knowledge, there has been no study on the Cu plasma levels in patients with lichen planus. The change in Cu plasma levels has been evaluated in many mucocutaneous autoimmune diseases like psoriasis [32], lupus erythematous [17], and pemphigus [33,34]. However, these reported findings are conflicting.

Increased copper/zinc ratio correlates positively with systemic oxidative stress status [16]; elevated Cu/Zn ratio has been considered as a prognostic and diagnostic biomarker of malignancy [35]. Certain studies have revealed a decreased Cu/Zn ratio in autoimmune diseases as a consequence of malnutrition [32,34]. The mean Cu/Zn ratios in erosive and patients were slightly raised compared with the controls, a difference not very significant.

In their study on 352 OLP patients, Chen et al observed a significantly higher frequency in iron deficiency (<60 mg/dL) in patients than in healthy participants. Furthermore, the mean blood iron levels were lower in patients than in controls, a difference which was only significant in women [23]. Challacombe observed an increased prevalence of a haematological abnormality in patients with oral lichen planus, but the prevalence of sideropenia did not significantly differ [25]. In this study, we were not able to find any association between serum iron and the disease.

We found that serum calcium levels increased significantly in the patient group. Calcium values were significantly elevated in erosive subgroup when compared to the control subjects. Our results are in contrast with a previous case control study on 36 OLP patients, where the total and ionized serum calcium was significantly lower in patients than in controls. Cubillos et al. evaluated the association of S100A7 gene polymorphisms with manifestations of psoriasis and its effect on plasma Ca levels [35]. Their results indicated significantly higher serum S100A7 protein and Ca values in psoriasis patients compared with the controls [35]. Wenzel et al. showed a statistically significant upregulation of S100A7 gene in three inflammatory skin disorders (lichen planus, psoriasis, atopic dermatitis) [36]. Another investigation on disturbed calcium homeostasis in palmoplantar pustulosis patients similarly showed an increase in the serum calcium of patients [37].

Magnesium plasma values did not change significantly in the patients of the present study. Our study seems to be the first to evaluate serum Mg in OLP patients. The results are in agreement with a previous work on lupus erythematous [17].

CONCLUSION

Trace element such as calcium may have a role in the ethiopathogenesis of OLP. However, other elements such as Zinc or Cu may influence OLP pathogenesis, which requires further evaluation on larger scales.

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Conflict of Interest: None declared.

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